

S/N 09/900,754

PATENT  
CONF NO: 4570



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Allen, Keith D.	Examiner:	Sullivan, Daniel M.
Serial No.:	09/900,754	Group Art Unit:	1636
Filed:	July 6, 2001	Docket No.:	R-372/75658.031700
Title:	Transgenic Mice Containing Tryptase Gene Disruptions		

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DECLARATION OF JOHN BURKE PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, John E. Burke, residing at 16357 E. Berry Avenue, Centennial CO 80015, hereby declare:

1. I am currently, and have been since 1998, the Attorney of Record for the Applicant and Assignee, Deltagen, Inc. I am listed on the originally filed Power of Attorney for the present application. From December 1996 to December 1999, I was Of Counsel with the law firm of Pillsbury Madison & Sutro (currently Pillsbury Winthrop) where I represented Deltagen with respect to intellectual property matters, including patent matters relating to their transgenic mouse program. From December 1999 until December 2001, I served as Deltagen's Vice President of Intellectual Property, where I supervised Deltagen's internal patent department. All of the applications, including the present application, covering the 750 lines of mice in DeltaBase were drafted by Deltagen's patent department. From December 2001 until April 2003, I served as Deltagen's Senior Vice President and General Counsel. From April 2003 through April 2005, I was a partner with the Denver office of Merchant & Gould, where I continued to represent Deltagen with regard to intellectual matters, including patent matters. I am presently employed as a Shareholder with the Denver office of the law firm of Greenberg Traurig, where I am

responsible for prosecution of Deltagen's patent portfolio relating to their transgenic mice program, including the present application.

2. I am familiar with the present application. I am familiar with the Office Action mailed May 12, 2005. I am aware that the Examiner has rejected the claims, in part, for allegedly failing to meet the utility and enablement requirements. I am aware that the Examiner has argued that the phenotypic differences observed in the transmembrane tryptase (mTMT) gene knockout mouse are not statistically significant.

3. I hereby declare that, as evidenced by the attached Exhibit, the subject matter of the present application, mTMT gene knockout mice, were compared with control mice of identical background. I further declare that when compared to such control mice, the mTMT gene knockout mice exhibit statistically significant phenotypic differences.

4. I hereby declare that the claimed mTMT gene knockout mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK.

5. I hereby declare that I have accessed Deltagen's internal web-based DeltaBase database to review the data derived from analyses of the claimed mice. I hereby declare that the attached Exhibit contains 4 pages, each representing a screen printout from DeltaBase. Pages 1-2 (a single web page that has been printed on two separate pages) describe the behavioral phenotypes for mTMT knockout mice (the printout refers to Gene 372 which is Deltagen's internal code for the mTMT gene, as indicated in the docket number of the instant case. The printout also refers to the gene as Tpsgl which is a synonym for mTMT). Pages 1-2 also describe how the mTMT knockout mice were generated. Specifically, pages 1-2 state that ES cells derived from the 129/SvJ x 129/Sv-+p+Tyr-c MgfSl-J/+ mouse substrain were used to generate chimeric mice. F1 mice were generated by breeding with C57BL/6 females. The resultant F1N0 heterozygotes were backcrossed to C57BL/6 mice to generate F1N1 heterozygotes. F2N1 homozygous mutant mice were produced by intercrossing F1N1 heterozygous males and females. Pages 1-2 also states that when compared to age-and gender-matched wild-type control mice, homozygous mutants mice displayed a difference in Prepulse

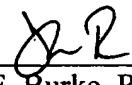
Inhibition (PPI), indicating a stimulus processing phenotype opposite to that seen in schizophrenic patients. Pages 1-2 also indicate the genotype of the -/- and +/+ wild-type control mice (table on right hand side of pages 1-2). It can be seen that all -/- and +/+ mice tested were F2N1 mice, *i.e.* the control mice were the wild-type progeny, and the mutant mice were the homozygous -/- progeny, of crosses between male and female mice heterozygous for the mTMT null allele.

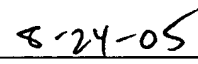
Page 3 presents the PPI findings in more detail, and also shows that the data were compiled from the F2N1 generations (data from one F2N0 mouse was subsequently excluded). All mice (wild-type, -/+, and -/-) were derived from the same ES cell line, 479. The ages and gender of the mouse are also indicated. Thus, the printout shows that -/-, -/+ and +/+ mice of the same strain (background), same F number, same N number, same gender, and same age were compared in the PPI test.

Page 4 presents the PPI results for the eleven -/- mice and the nine wild-type control mice of page 3. Page 4 also provides the 1-*p* values for the differences between the wild-type control and -/- mice. It can be seen that for the PPI measured captioned "PPI 90/120" (the % reduction in the startle response to a 120dB stimulus that is observed with a 90dB prepulse), the difference between wild-type control and -/- mice is highly statistically significant, with a 1-*p* value of 0.98.

6. In summary, the attached Exhibits show that the -/- mice were compared with control mice of identical age, gender, and background (strain) in the PPI test. The attached Exhibits also show that the difference between the PPI 90/120 results for -/- mice and +/+ mice is statistically significant.

7. I further declare that all statements made herein of my own knowledge are true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

  
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John E. Burke, Reg. No. 35,836

  
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Date

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Gene: 372 Name: **Protease** Subfamily: **Serine Protease** Alternative Names:
Nucleotide Sequence Accession: **AF075523** GI: 6108030 External Links: [Select External Database](#)

### Behavior

Changes related to genotype:

Homozygous mutant mice displayed significantly increased Prepulse Inhibition (PPI) with a 90dB prepulse.

Homozygous mutant and wild-type control mice were evaluated for phenotypic changes by testing on six behavioral tasks: Open field test, Tail suspension test, Rotarod test, Hot plate test, Startle/PPI, and Metrazol test.

Mouse ID numbers are as follows:

12 homozygous mutant males (65426, 65428, 65431, 65435, 66751, 66752, 66755, 66756, 72724, 74182, 74190, 74191)

9 wild-type control males (65424, 65430, 66753, 72730, 72731, 74183, 74185, 74188, 74196)

ES cells derived from the 129/SvJ x 129/Sv+Tyr-c MgfSl-J/+ mouse substrain were used to generate chimeric mice. F1 mice were generated by breeding with C57BL/6 females. The resultant F1N0 heterozygotes were backcrossed to C57BL/6 mice to generate F1N1 heterozygotes. F2N1 homozygous mutant mice were produced by intercrossing F1N1 heterozygous males and females.

#	Sex	Genotype	F Gen.	N Gen.	Age	Validity	Release
65426	Male	-/-	2	1	69	V	T
65426	Male	-/-	2	1	78	V	T
65428	Male	-/-	2	1	69	V	T
65428	Male	-/-	2	1	78	V	T
65431	Male	-/-	2	1	69	V	T
65431	Male	-/-	2	1	78	V	T
65435	Male	-/-	2	1	69	V	T
65435	Male	-/-	2	1	78	V	T
66751	Male	-/-	2	1	71	V	T
66751	Male	-/-	2	1	78	V	T
66752	Male	-/-	2	1	71	V	T
66752	Male	-/-	2	1	84	V	T
66755	Male	-/-	2	1	67	V	T
66755	Male	-/-	2	1	74	V	T
66756	Male	-/-	2	1	67	V	T
66756	Male	-/-	2	1	80	V	T
72724	Male	-/-	2	1	70	V	T
72724	Male	-/-	2	1	86	V	T
74182	Male	-/-	2	1	71	V	T
74182	Male	-/-	2	1	83	V	T
74191	Male	-/-	2	1	67	V	T
74191	Male	-/-	2	1	79	V	T
65424	Male	-/-	2	1	69	V	T

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Gene: 372

Name: Tpsg1

Family: Protease

Subfamily: Serine Protease

Alternative Names

Nucleotide Sequence

Accession: AF025523

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66736 Male -/ - 2 1 80 V T

72724 Male -/ - 2 1 70 V T

72724 Male -/ - 2 1 86 V T

74182 Male -/ - 2 1 71 V T

74182 Male -/ - 2 1 83 V T

74191 Male -/ - 2 1 67 V T

74191 Male -/ - 2 1 79 V T

65424 Male +/+ 2 1 69 V T

65424 Male +/+ 2 1 78 V T

65430 Male +/+ 2 1 69 V T

65430 Male +/+ 2 1 78 V T

66753 Male +/+ 2 1 71 V T

66753 Male +/+ 2 1 78 V T

72730 Male +/+ 2 1 69 V T

72731 Male +/+ 2 1 69 V T

72731 Male +/+ 2 1 79 V T

74183 Male +/+ 2 1 71 V T

74183 Male +/+ 2 1 83 V T

74185 Male +/+ 2 1 72 V T

74185 Male +/+ 2 1 84 V T

74188 Male +/+ 2 1 72 V T

74188 Male +/+ 2 1 84 V T

74196 Male +/+ 2 1 68 V T

74196 Male +/+ 2 1 80 V T

Behavior Findings:

ES cells derived from the 129/SvJ x 129/Sv+pr-Tyr-c MgfSl-J/+ mouse substrain were used to generate chimeric mice. F1 mice were generated by breeding with C57BL/6 females. The resultant F1N0 heterozygotes were backcrossed to C57BL/6 mice to generate F1N1 heterozygotes. F2N1 homozygous mutant mice were produced by intercrossing F1N1 heterozygous males and females.

When compared to age- and gender-matched wild-type control mice, homozygous mutants mice displayed a difference in PPI, indicating a stimulus processing phenotype opposite to that seen in schizophrenic patients.

There were no other genotype-related or biologically significant differences noted between mutant and wild-type control mice for any of the parameters evaluated during behavior testing.

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